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Dihydroetorphine: A Potent Analgesic: Pharmacology, Toxicology, Pharmacokinetics, and Clinical Effects

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ABSTRACT

Dihydroetorphine (DHE) is one of the strongest analgesic opioid alkaloids known; it is 1000 to 12,000 times more potent than morphine. Several *in vitro* and *in vivo* studies have shown that DHE is a selective μ-opioid receptor (OP_3) agonist that also binds and activates all human recombinant μ-, δ-, and κ-opioid receptors (OP_3, OP_1, and OP_2). The onset of the analgesic effect of DHE in rodents is rapid, 5 to 15 min after parenteral administration; the duration of action is short, the analgesic effect disappears within 120 min after administration. By oral administration much higher doses of DHE are required to produce analgesic effects. These characteristics are accounted for by the pharmacokinetic properties of DHE in the rat, namely, by rapid distribution of DHE from the injection site to the brain and rapid metabolism by glucuronidation in the gut and liver followed by elimination into the bile. Continuous infusion and repeated administration of DHE lead to the development of tolerance to analgesia, physical dependence, and a rewarding effect in normal rats but not in animals with formalin-induced inflammation. Although formalin-induced inflammation is only one type of pain stimulus, these findings suggest that DHE addiction would be observed only in the case of pain-free conditions. Clinical reports in China show that sublingual doses of DHE, 20 to 180 μg, produce a potent analgesic effect with only mild side effects, including dizziness, somnolence, nausea, vomiting, constipation, and shortness of breath. To improve the short-lasting effect following sublingual administration, transdermal delivery of DHE via a patch has been investigated. The patch formulation of DHE produces continuous analgesic effect with minimal physical dependence and rewarding effect in rats suffering from chronic pain. This patch formulation, which is very suitable for DHE, may be viable for the treatment of severe pain and is likely to improve patients' quality of life.

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INTRODUCTION

Dihydroetorphine (DHE), 7,8-dihydro-7α-[1-(*R*)-hydroxy-1-methylbutyl]-6,14-*endo*-ethanotetrahydro-oripavine (Fig. 1a), was synthesized by Bentley and Hardy in 1967 (5). DHE is the strongest analgesic opioid alkaloid known. DHE produces an extraordinarily strong analgesia; it is 1000 to 12,000 times more potent than morphine (MOR) (1,5,54, 62). In China, DHE was first used clinically for pain relief in 1981 and was registered as an analgesic for severe pain in 1992. Unexpectedly, abuse of DHE increased rapidly soon after it was marketed. Since 1993 the use of DHE has been controlled by the Chinese government. Epidemiological studies show that the majority of abusers take DHE to avoid the withdrawal syndrome of heroin or other opiates (6,25) because of its psychological dependence-producing properties, low cost, and failure of some countries to control it (69). In March 1999, the United Nations decided to include DHE in Schedule I of the 1961 Convention on Narcotic Drugs (57). Subsequently, DHE has been used clinically for pain relief under restricted conditions (60,78).

In clinical and experimental animal studies, the analgesic effect and dependence potential of DHE has been thoroughly investigated. However, the disposition of DHE is poorly understood because there is no quantitative method with sufficient sensitivity to detect DHE in biological samples due to the extremely low dose of DHE administered. Huang et al. (16) administered tritium-labeled DHE to rodents and measured the radioactivity in blood and brain. Radioactive DHE in blood and brain indicates the total amount of unchanged drug and metabolites. However, to understand its disposition in relation to its pharmacological effect, unchanged DHE, which is the pharmacologically active form in the body, must be measured. Recently, we developed an extremely sensitive method to detect unchanged DHE in biological samples using liquid chromatography, tandem mass spectrometry (LC-MS-MS) (38). Furthermore, we studied the pharmacokinetic and pharmacodynamic properties of DHE in rats and developed a useful pharmaceutical formulation to produce the potent analgesic activity while preventing the development of dependence (37,39–41).

MOR is the most commonly used opioid analgesic for pain relief, and its oral daily dose (20 to 1000 mg) is relatively high (44). On the other hand, DHE produces rapid analgesic effects at an extremely low dose, 20 μg sublingually in humans (60,78). This property suggests that it should be possible to use DHE in an ideal pharmaceutical formulation, such as long-acting transdermal therapeutic system, which is not possible with other analgesics. Although addiction is a real problem with DHE, it needs to be reappraised in terms of its analgesic profile and potential to cause dependence. This paper reviews the results of preclinical and clinical studies dealing with the pharmacology, toxicology, pharmacokinetics, and pharmaceutical formulation of DHE.

PHARMACOLOGY

Discovery

Bentley and Hardy (5) synthesized alcohols of 6,14-*endo*-ethenotetrahydro-oripavine analogs and compared their analgesic effects. They found that the 7α-[1-(*R*)-hydroxy-1-methylbutyl] group is required to produce the potent analgesic effect and, subsequently synthesized DHE, the strongest analgesic known. As an analgesic DHE is 12,000 times more potent than MOR. Etorphine (ETR), 7α-[1-(*R*)-hydroxy-1-methylbutyl]-6,14-*endo*-ethanotetrahydro-oripavine (Fig. 1b), is structurally related to DHE, but is only 3200 times more potent than MOR (5). Since ETR has been included in Schedule I of the 1961 Convention on Narcotic Drugs (69), many investigators thought that DHE would be liable to abuse. In 1982, Hang and Qin (14,15) found that DHE produced a powerful analgesic effect with only mild physical dependence. Their observations led to the use of DHE in China for pain relief and for suppression of opioid withdrawal syndrome (69).

Opioid Receptor Selectivity

Several *in vitro* and *in vivo* studies have shown that DHE is a highly selective agonist of μ-type opioid receptors. Wang et al. (62) investigated the selectivity of DHE and ETR for opioid receptors by radioligand binding assay using rat brain membrane and by inhibiting their analgesic effect with a selective receptor antagonist in the mouse. The inhibitory constants (K_i) of DHE for the binding of the μ-selective ligand [D-Ala^2,*N*-Me-Phe^4,Gly-ol^5]-enkephalin (DAMGO) to rat brain membrane (9.69×10^{-12} M) is much lower than that of ETR (3.62×10^{-10} M). The relative affinity ratios of DHE and ETR for μ-, δ-, and κ-opioid receptors are 333:1:1 and 10:2:1, respectively. The half maximum dose for the analgesic effect (ED_{50}) of DHE and ETR is 1.05 and 2.21 ng per mouse after intracerebroventricular (i.c.v.) injection, respectively. The analgesic effect of DHE in mouse is selectively inhibited by pretreatment with the μ-selective antagonist β-funaltrexamine, while that of ETR is inhibited by pretreatment with β-funaltrexamine and the κ-selective antagonist nor-binaltorphimine. These results suggest that DHE is a more potent and selective agonist of the μ-opioid receptor compared with ETR *in vitro* and *in vivo*. Other studies in rodents have shown that the analgesic effects produced following DHE administration are inhibited by pretreatment with the μ-selective antagonist naloxone, but not by the δ- and κ-selective antagonists, naltrindole and nor-binaltorphimine (1,55). Kamei et al. (20) have reported that the analgesic effect of DHE is mediated by both μ_1- and μ_2-opioid receptors in the mouse using the μ_1-selective antagonist naloxonazine.

In contrast to these findings, several *in vitro* studies suggest that DHE and ETR have nonselective agonist properties. Niwa et al. (36) reported that DHE and ETR have the same binding affinity for μ-, δ-, and κ-opioid receptors and a similar inhibitory effect on the forskolin-stimulated adenylate cyclase activity. Their study was carried out on Mongolian gerbil cerebellum, guinea pig forebrain, and human placenta P3 fraction to determine the selective binding and activation of μ-, δ-, and κ-opioid receptors, respectively. Similarly, nonselective affinity and activity of DHE for opioid receptors have been observed in a study using cloned human μ-, δ-, and κ-opioid receptors expressed in Chinese hamster ovary (CHO) cells (21). The inhibitory effects of DHE and ETR on mouse sensory dorsal-root ganglion neurons also appear to be nonselective as far as the three opioid receptor subtypes are concerned (45). In the case of C6 glioma cells transfected with cDNA of rat μ- and δ-opioid receptors, DHE and ETR fully stimulate GTPγS-binding to the μ-type cell membrane and partially stimulate binding to the δ-type cell membrane (23). In addition to *in vitro* experiments, it has been reported that DHE suppresses capsaicin-induced cough in the mouse and that this effect is inhibited by μ- and κ-opioid receptor antagonists, but not by δ-opioid receptor antagonists (18). These differences in the receptor-selectivity of DHE may reflect species and organ differences in the receptor conformation and activation, including G-protein interactions, adenylate cyclase regulation, phospholipase C activation, and protein kinase A-dependent ionic conductance, as well as by an interaction between receptors.

The DTNB-index is the ratio of the affinity of a compound to 5,5′-dithiobis-(2-nitrobenzoic acid) (DTNB), an SH-group blocker; it is used to determine whether a compound is an agonist or an antagonist. The index indicated that DHE has both agonist and antagonist properties, in contrast to ETR, which has only agonist effects (36). However, Wang and Qin (63) have reported that the affinity of DHE for rat brain membrane is markedly reduced to 1/40 by adding sodium ions and guanine nucleotides, suggesting that DHE could be a full agonist. Lee et al. (23) have also reported that DHE and ETR are full agonists for expressed μ-opioid receptors, although reductions of their binding affinity induced by NaCl and 5′-guanylylimido-diphosphate are less than 2-fold.

Analgesic Effect

DHE produces a potent analgesic effect in the mouse, rat, rabbit, dog, and monkey (14,16). The *in vivo* analgesic effects of DHE are measured by the antinociceptive effect using the tail-flick, tail-pinch, and hot-plate tests, the chemical agent writhing test and the electrical stimulation test (1,14,16,54). Aceto et al. (1) have reported that the ED_{50} values of DHE in mice measured by the tail-flick, hot-plate, and phenylquinone tests were very similar (0.15, 0.1, and 0.2 μg/kg, respectively) while those of ETR were different (2, 1, and 0.4 μg/kg, respectively). Quick nociception by heating and pressing are mediated through activation of A-delta fibers, while gradual nociception by chemical agents is mediated by C-polymodal fibers (34). Site-specific distribution of drug may be the reason for the different ED_{50} values of DHE and ETR.

Tokuyama et al. (54) examined the duration of the analgesic effect of DHE and MOR, by various routes of administration, in mice by the tail-pinch test. The analgesic effects of DHE developed rapidly, reaching the maximum within 15 min after oral (p.o.), intraperitoneal (i.p.), subcutaneous (s.c.), and intravenous (i.v.) administration and within 5 min after intrathecal (i.t.) and i.c.v. injection. The effect disappeared within 90 min after administration of DHE. The appearance and disappearance of the analgesic effect of DHE are relatively rapid in comparison with those of MOR in mice. The ED_{50} values calculated from an area under the analgesic effect-time curve (AUC) after p.o., i.p., s.c., i.v., i.t., and i.c.v. administration were 818.0, 8.2, 5.8, 5.3 μg/kg, 68.5, and 87.5 ng/mouse, respectively, and the ratio of the ED_{50} values of MOR to DHE were 96, 1092, 1421, 1250, 10, and 18, respectively (Table 1). The authors suggested that the route-of-administration-dependent ED_{50} ratio of MOR to DHE could be caused by a difference in the absorption and disposition of DHE and MOR in mice. In the rat, the analgesic effect, measured by the acetic acid writhing test, reached a maximum at 30 min and disappeared within 120 min after s.c. injection of 0.5 μg/kg DHE (16). ETR (2 μg/kg s.c.) produced the same analgesic effect as DHE (0.15 μg/kg s.c.); their duration of action was apparently different from that of MOR; its effect lasted for 80 min (1).

Tolerance to Analgesia

In an animal experiment, the analgesic effect mediated by μ-receptor agonists, such as MOR, is reduced with repeated administration (11). Tokuyama et al. (55) reported that the analgesic effect of DHE is significantly reduced in mice after daily oral administration for 5 days. Furthermore, repeated doses of DHE for 5 days induced a reduction in the analgesic effect of MOR in mice and vice versa. Kamei et al. (19) reported that in mice the analgesic effect of MOR is reduced to the greatest extent at 4 h after pretreatment with DHE, i.p., and returns to the control level at 24 h. Choe and Smith (10) reported that the analgesic effect of DHE is reduced in rats following infusion of fentanyl. These results indicate that DHE and other μ-receptor agonists develop a cross-tolerance through activation of the same receptor.

We also found that the analgesic effect of DHE is reduced gradually. An induction of tolerance was observed during a 24-h continuous infusion and 4 days of repeated s.c. injections in the rat (37). Interestingly, the appearance of tolerance to DHE analgesia is delayed or abolished in rats pretreated with formalin, injected into the surface of the hind paw at 24 h before DHE, a model of chronic pain. This phenomenon has been also observed with MOR and other opioids by several investigators, who demonstrated that the tolerance to analgesia is reduced by pain stimuli induced by formalin or carrageenan (51,59). Most notably, these results are consistent with clinical experience in which chronic severe pain is successfully relieved by "high-ceiling" MOR (42). These results indicate that in clinical situations, in patients with chronic pain, tolerance to the analgesic effect of DHE may not develop, as is the case with other opioids.

There are many *in vitro* and *in vivo* reports regarding the mechanism for tolerance to analgesia developed by DHE. Wang and Qin (64) reported that μ-opioid receptor mRNA levels are reduced in the rat midbrain after only 3 days of treatment with DHE, and they are reduced in the hippocampus and striatum after 7 and 21 days of treatment, respectively. Chen et al. (8) showed that cAMP levels in the hypothalamus, striatum, and cerebral cortex are significantly reduced in the DHE-tolerant mouse, whereas glutamic acid, aspartic acid, and GABA levels are increased in the brain. Keith et al. (22) reported the internalization of μ-opioid receptors in the rat parietal cortex, habenula, and striatum within 30 min of i.p. injection of ETR. In an *in vitro* study, DHE lead to phosphorylation and desensitization of human μ-opioid receptors expressed in CHO cells (75) and rapid internalization of μ-opioid receptors expressed in HEK293 cells (22).

Other Effects

Neuropathic pain is typified by an increased sensitivity to painful stimuli, hyperalgesia, and the perception of normally innocuous stimuli as painful (allodynia). Such pain is known to be resistant to the treatment with opioids, like MOR (35). Martin et al. (32) re-

TABLE 1. ED_{50} values for analgesic effects of dihydroetorphine (DHE) and morphine (MOR) in mice by various routes of administration

	ED_{50} values for analgesic effect		
Route of administration	DHE	MOR	Ratio MOR/DHE
Oral	818.0 μg/kg	78.1 mg/kg	96
Intraperitoneal	8.2 μg/kg	8.9 mg/kg	1.092
Subcutaneous	5.8 μg/kg	8.2 mg/kg	1.421
Intravenous	5.3 μg/kg	6.7 mg/kg	1.250
Inthrathecal	68.5 ng/body	0.9 μg/body	10
Intracerebroventricular	87.5 ng/body	1.2 μg/body	18

Data from ref. 54.

ported that at 0.2 μg/kg i.v. DHE has an antiallodynic action. In rats following ligation of the fifth and sixth lumbar nerves, a model of neuropathic pain, DHE is ca. 7440 times more potent than MOR. Hopefully, DHE would offer a unique opportunity as a treatment for neuropathic pain.

DHE and ETR suppress the withdrawal syndrome in opioid addicts (17,43,66). DHE also suppresses withdrawal signs in MOR-dependent rats and monkeys (1,61). Martin et al. (33) reported that DHE substituted for heroin in rats trained in self-administration, in this test it was 1,500 to 3,000 times more potent than MOR. DHE has not yet been used for substitution therapy in opioid abusers.

It is well known that MOR has both humoral and cell-mediated immunosuppressive effects, such as suppression of the cytolytic effects of natural killer cells (68), T- and B-cell mitogen-stimulated lymphocyte proliferation (3), and cytokine production (31). Wu et al. (73) reported that DHE, at 24 and 128 μg/kg s.c., dose-dependently reduced splenic lymphocyte proliferation and interleukin-2 production-induced by concanavalin A or lipopolysaccharide in mice. These responses were blocked by naloxone or by α-adrenoceptor antagonist, phentolamine, but not by β-adrenoceptor antagonist, propranolol. Moreover, by subchronic injection, 4 times a day for 14 days, either DHE or MOR reduced delayed-type hypersensitivity, generation of antibody-forming cells, and the ratio of helper T-cell to suppressor T-cell (71). As an immunosuppressant, DHE is almost 4000 times as potent as MOR.

ADVERSE EFFECTS

Physical Dependence

It has been recognized that DHE has minimal physical dependence properties in spite of its extremely potent analgesic effect (14,15,55). There are some reports regarding the mechanism of this disparity between its analgesic effect and development of dependence (26,45). In *in vitro* studies using mouse sensory dorsal-root ganglion neurons, DHE activated G-protein–coupled opioid receptors. This effect is unlike the bimodal activation effect of MOR (45). At low concentrations (less than 1 nM), MOR prolongs the duration of the action potential (APD) via activation of stimulatory G-protein (Gs)–coupled opioid receptors, and at relatively higher concentrations (μM) it shortens APD via activation of inhibitory G-protein (Gi/Go)–coupled opioid receptors. However, DHE only activates inhibitory opioid receptors at lower concentrations (pM). Liu et al. (26) also demonstrated that low-pH treatment of neuroblastoma cells, which deletes Gs-protein function, has no effect on the inhibitory action on adenylate cyclase elicited by DHE. It has been suggested that activation of excitatory G_s-coupled opioid receptors results in the development of physical dependence to opioids, others than DHE.

Only following continuous exposure by infusion (2,37,79) and short-term repeated injections (53) can DHE produce physical dependence in rats. A 24-h infusion of DHE and MOR at more than 10 times the ED_{50} induced naloxone-precipitated body weight loss (37,79). Aceto et al. (2) also described a typical withdrawal syndrome after 4 days of escalating continuous infusion in rats. However, they reported that intermittent and escalating doses of DHE for 42 days showed few withdrawal signs in rhesus monkeys (1). Tokuyama et al. (53) showed that the naloxone-precipitated withdrawal symptoms were significantly increased when DHE was administered by five 5 repeated i.p. injections at intervals of less than 2 h and naloxone injected within 1 h after the last injection of DHE. These results suggested that DHE produces physical dependence only by continuous exposure, this may be due to the rapid abolition of the analgesic effect of DHE and its pharmacokinetic properties described below.

Rewarding Properties

Since DHE addiction was found in China, it has been confirmed that DHE induces a potent reinforcing effect and discriminative stimulus effect in the drug self-administration test in rats and monkeys (4,33,65,72). The conditioned place preference (CPP) test, which distinguishes between rewarding and adverse properties of drugs (56), also confirmed the rewarding effect elicited by repeated DHE administration in rats (28,29,37). These results account for the potential for DHE abuse, which actually occurred in China. We found that rats conditioned by repeated s.c. injections of DHE 2 μg/kg and MOR 10 μg/kg exhibited a significant preference for the drug-paired place (37). Liu and Zhang (29) have also reported that rats conditioned by twice daily repeated s.c. injections of DHE 0.05 μg/kg for 5 days exhibited a significant drug preference, and DHE reward was suppressed by treatment with the dopamine D1 receptor antagonist Sch-23390. It is known that the mesolimbic dopamine system and its terminals in the nucleus accumbens are involved in the *craving effects* of drugs of abuse (46). Suzuki et al. (50,52) showed MOR reward is reduced by the *N*-methyl-D-aspartate receptor antagonist ifenprodil and the δ-opioid receptor antagonist nartrindole. However, no one has investigated whether the DHE reward is related to other opioid systems and the neural excitatory amino acid system.

Attenuation of Dependence Liability in Animals Suffering from Pain

There are some reports that the withdrawal behavior and rewarding effects of MOR are reduced in animals suffering from formalin-induced pain (58,51). Although formalin injection induces acute pain and durable inflammation in rats, which is one type of pain stimulus, these results support the fact that no opioid-addicted patients are being treated for pain relief (12,42). Other commercially available opioids also attenuate the development of tolerance, physical dependence, and rewarding properties in a chronic pain model. Suzuki et al. (52) reported that the κ-opioid antagonist nor-binaltorphimine suppressed the reduction in MOR reward in rats with formalin-induced inflammation. From this, they suggested that chronic pain stimuli may induce activation of the κ-opioid system, and this induction causes the disappearance of the opioid reward.

We confirmed that naloxone-precipitated body weight loss and the rewarding effect of DHE elicited by a 24-h continuous infusion and 4 days of repeated s.c. injections of DHE is reduced in such rats (37). This result indicates that, in clinical situations, DHE is liable to produce physical dependence and reinforcing properties only in the case of pain-free conditions, although DHE can be used safely to relieve pain.

Other Adverse Effects

It has been reported that MOR produces sedation, respiratory depression, constipation, cardiovascular dysfunction, emesis, flushing, and urination difficulties in humans (44). Huang and Qin (14) reported that DHE produces central nervous system depression, with ED_{50} values of 0.86 μg/kg s.c. for respiratory depression in rabbits, 13 μg/kg s.c. for catalepsy in mice, and 50 μg/kg s.c. for loss of righting reflex in mice (Table 2). The ratio of the ED_{50} values of DHE for respiratory depression to the analgesic effect as a therapeutic index are 2, 20, and 28 in rabbit, dog, and monkey, respectively. This value in rabbit is two times higher than that of MOR. Choe and Smith (10) reported that DHE produces severe sedation, and the ED_{50} values for catalepsy and loss of righting reflex are 0.55 and 0.81 μg/kg s.c., respectively, in the rat (Table 2). However, in the mouse, the ED_{50} value of DHE for the loss of righting reflex is relatively high, 50 μg/kg s.c. (16). These findings suggest that the therapeutic index of DHE in mouse is higher than that in rat.

Wang et al. (67) reported that DHE, administered as three i.m. injections of 1 or 2 μg/kg to pregnant mice did not affect their parturition. However, DHE at 4 μg/kg and MOR at 200 μg/kg caused cyanosis in 14% and 23% of newborn mice, which is two-fold and three-fold higher than the 7.4% in control mice. Yin et al. (74) reported that repeated injection of DHE to pregnant mice affected body weight, physiologic landmarks, reflex development and sensory function, movement coordination, learning and memory, and activity in the offspring in a dose-independent manner over the range 0.05–50 μg/kg.

PHARMACOKINETICS

Huang et al. (16) investigated the pharmacokinetic properties of DHE using tritium-labeled drug in the mouse. Radioactivity in the blood reaches a maximum of 0.25–0.31 ng/ml at 5 to 10 min after sublingual administration of 2.36 μg/kg [^{3}H]DHE and is then biphasically eliminated with half-lives of 2.5 and 41.7 min. Radioactivity in the brain is slightly higher than in the blood (0.29–0.37 ng/ml at 10 to 20 min), and this is eliminated with the same order of half-lives as in blood. In a dose-escalating study of DHE in mice reported by Yuan et al. (76), the maximum concentration (C_{max}) and AUC values of radioactivity in blood are proportional to the dose from 1 to 16 μg/kg given by s.c. injection, and the elimination half-lives (20 to 37 min) are independent of the dose. The radioactivity distributes to the kidney at the highest concentration (9-fold that in blood) and to lung, intestine, liver, and heart at levels equal to or up to 3-fold more than blood. In mice, after s.c. injection of [^{3}H]DHE, 2 μg/kg, 40% of radioactivity is excreted

TABLE 2. ED_{50} values for analgesic and adverse effects of DHE and MOR in experimental animals

	DHE (s.c., μg/kg)			MOR (s.c., mg/kg)
	Rabbit[a]	**Dog**[a,c]	**Monkey**[a]	**Rabbit**[a]
Analgesic effect	0.43[d]	0.5	0.1[d]	4.94[d]
Respiratory depression	0.86 (2.0)	10 (20)	2.86 (28)	5.15 (1.0)
	Mouse[a]	**Rat**[b]		**Mouse**[a]
Analgesic effect	0.47[e]	0.9[f]		2.95[e]
Catalepsy	13 (28)	0.55 (0.6)		66 (22)
Loss of righting reflex	50 (106)	0.81 (0.9)		>400 (>136)

Figures in parenthesis indicate the ED_{50} ratios of analgesic to adverse effects.
[a]From ref. 14. [b]From ref. 10. [c]DHE was given i.m. in dogs.
Analgesic effects are measured as antinocicpetion by [d]K^+ iontophoresis; [e]55°C hot-plate; and [f]radiant heat.

in the urine within 72 h. In an *in vitro* autoradiographic study of the rat brain by Yuan et al. (77), the radioactivity was found to be highly bound to the striatum, nucleus accumbens, I and III laminae of the cerebral cortex, thalamus, habenula, amygdaloid complex, interpeduncular nucleus and locus caeruleus, tissues that have μ-opioid receptors. However, it is important to remember that the radioactivity in blood and brain indicates the total amount of unchanged DHE and its metabolites. To understand its disposition in relation to its pharmacological effect, the unchanged DHE, which is the pharmacologically active form in the body, must be measured separately.

Recently, we developed an extremely sensitive method to detect unchanged DHE and dihydroetorphine glucuronide (DG) in biological samples using LC-MS-MS and evaluated the pharmacokinetic and pharmacodynamic properties of DHE in rats (38,39). The elimination half-life of plasma DHE was 37.2 min after an i.v. injection of DHE, 2 μg/kg, (Table 3). The plasma concentrations of DG, which is the pharmacologically inactive form, increase over the DHE concentrations and then fall in parallel with DHE. Ninety percent of the DHE is excreted as DG in the bile after i.v. injection in bile-duct cannulated rats. Other metabolites of DHE are not known. The brain DHE concentration reaches a maximum within 6 min, 5.2 times higher than the plasma DHE concentration. The bioavailability of DHE after intracutaneous (i. c.), s.c., i.p., and p.o. administration is 71, 80, 17, and 0.37%, respectively. Serum protein binding of DHE is 83.4% and this is not influenced by the DG concentration in serum. *In vitro* glucuronidation of DHE occurs in the liver, intestine, and kidney. These results suggest that the rapid onset and elimination of the potent analgesic effect and lower dependence potential of DHE are closely related to the rapid elimination of DHE.

CLINICAL STUDIES

DHE was first clinically tested for pain relief and suppression of opioid withdrawal syndrome in the 1980s. In 1992, in China, the sublingual tablet contained 20 μg DHE was registered as an analgesic for severe pain. Wu and Sun (70) examined the clinical results

TABLE 3. Pharmacokinetic parameters after various routes of administration of DHE in rats

Parameters	
A. Intravenous injection, 2 μg/kg	
Half-life of DHE, early phase, in plasma ($t_{1/2\alpha}$)	3.77 min
Half-life of DHE, late phase, in plasma ($t_{1/2\beta}$)	37.2 min
AUC of DHE in plasma	66.3 (ng · min)/mL
AUC of DG in plasma	117 (ng · min)/mL
AUC of DHE in brain except cerebellum	322 (ng · min)/mL
B. Extravascular administration	
Bioavailability, intracutaneous injection, 2 μg/kg	70.8%
Bioavailability, subcutaneous injection, 2 μg/kg	79.8%
Bioavailability, intraperitoneal injection, 10 μg/kg	16.7%
Bioavailability, oral, 200 μg/kg	0.37%

Data from ref. 39.

with DHE in the treatment of 103 patients with moderate-to-severe cancer pain. 20 to 40 μg of sublingual DHE produced moderate to complete relief of the cancer pain. The average onset of action for DHE was 20 min and the average duration of action was 3.9 h. There was no relationship between age, sex, and site of the cancer pain to the analgesic effect of DHE, but pain-relief in patients with bladder cancer was poor. The reported clinical side effects of DHE were dizziness (72%), somnolence (60%), nausea (30%), vomiting (16.5%), constipation (5%), and shortness of breath (8%). In two patients, the administration of DHE had to be stopped due to side effects. Chen et al. (9) reported the use of DHE, 20 to 40 μg, 1 to 3 times/day for less than 21 days for pain relief. The highest dose (DHE 180 μg) was well tolerated. Li et al. (24) reported that sublingual DHE, 800 to 2000 μg, produced side effects in 32% of cancer patients.

During February and March 1993, DHE consumption in China, both recreational and medicinal, increased sharply before it was brought under control (9). Liu et al. (25) carried out an epidemiological study involving 291 DHE abusers who were admitted for detoxification. They showed that the main reasons for DHE use were withdrawal avoidance, euphoria, and relief from anxiety. Only 5% of abusers used DHE as medical treatment. Severe withdrawal symptoms included insomnia, sweating, restlessness, ache, gooseflesh, sickness, yawning, runny eyes, poor appetite, and weakness. DHE abusers used the drug at a habitual dose of 1,228 μg/day, which is more than 10 times the initial dose. Such a high dose was used, because of the duration of action needed to suppress withdrawal symptoms. DHE withdrawal symptoms occur earlier and are milder; they disappear faster and detoxification is easier than with other opioids (6). Since 86% of abused DHE is supplied by the black market (25), its use decreased rapidly after governmental control of DHE was instituted in April 1993 (9). Factors involved in the development of tolerance and abuse of drugs by humans include not only physical dependence, and rewarding properties, but also mode of administration, propensity for risk taking and conditioned stimuli. Currently, DHE is widely used to relieve pain in China (60,78).

By sublingual administration DHE is a highly potent analgesic. By oral administration DHE is much less potent; the effective dose is 25 to 75 μg for pain relief (70). The lower potency of oral DHE has also been observed in experimental animals (54); it has been suggested that the poor oral efficacy is due to the first-pass metabolism in the gut and liver (39). There is no information on the disposition of DHE in humans because of the lack of a sufficiently sensitive analytical method to measure its plasma concentrations (27,30). However, our sensitive LC-MS-MS method can measure the pharmacologically effective concentrations of DHE in rat plasma (38). We propose that clinical therapeutic and toxic plasma concentrations of DHE could be monitored by this sensitive method so that the therapeutic use of DHE could be optimized.

PHARMACEUTICAL FORMULATION

Since oral DHE has been shown to be ineffective in clinical trials, DHE is administered in the clinic sublingually (70). The sublingual administration DHE has a rapid onset of action (within 20 min), but its duration of action is relatively short (less than 4 h). Therefore, DHE has to be administered several times per day for continuous pain relief. In order to improve the poor oral availability and the short duration of its analgesic effect, transdermal delivery is considered potentially suitable for the clinical use of DHE. There are many reports on the usefulness of transdermal delivery of opioid analgesics, such as MOR (49), buprenorphine (48), and fentanyl (47).

Guo et al. (13) reported that DHE passes through snake skin *in vitro*. Chen et al. (7) reported the transdermal delivery of DHE using a drug-reservoir system with a permeation-enhancer, azone. This delivery system produces stable blood concentrations and an analgesic effect lasting 32 h in the rat. We have examined the transdermal delivery of DHE using a drug-dispersed patch formulation (40). In a patch DHE passes through excised abdominal and dorsal skin of rats. During abdominal (20 μg/0.28 cm^2) and dorsal (35 μg/0.50 cm^2) applications of the DHE patch, the plasma DHE concentrations and analgesic effect are maintained at a suitable level (0.2 to 1.2 ng/ml) until the patch is removed at 8 to 24 h later. Furthermore, we formulated the DHE patch with a diffusion-controlling membrane to maintain suitable therapeutic concentrations of DHE unaffected by skin damage (41).

Continuous administration by transdermal formulations may induce tolerance to analgesia and/or a potential for dependence. We investigated, whether our DHE transdermal patch could lead to tolerance to analgesia and could produce dependence in the rat (37). We found that tolerance and dependence could develop with the use of DHE patch in normal rats, but not in animals with formalin-induced inflammation. These results indicate that transdermal application of DHE has a potential for tolerance and dependence if there is no pain stimulus, but not if there is chronic pain. This patch formulation, most suitable for DHE, may contribute to the treatment of conditions involving severe pain and may improve the quality of life in terminally ill patients.

CONCLUSIONS

DHE is one of the strongest analgesic opioid alkaloids known. Several *in vitro* and *in vivo* studies have shown that DHE is a selective μ-opioid receptor agonist, although it binds and activates all subtypes of human recombinant opioid receptors. The onset of its analgesic action is rapid, its duration of action by systemic and nonsystemic administration to rodents is rather short and it is largely ineffective by oral administration. These characteristics are accounted for by its pharmacokinetic properties. Continuous exposure to DHE results in tolerance to analgesia, physical dependence, and a rewarding effect in normal animals, but not in rats with formalin-induced inflammation. In clinical reports, by sublingual administration DHE produces a potent analgesic effect with only mild side effects. In rats with inflammatory pain transdermal delivery of DHE by patch produces continuous analgesic effect with minimal physical dependence.

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